Remarks

Claims 1-52 are pending. Claims 5-15, 17, 18, 21-27, 29, 31, 35, and 37-52 have been withdrawn. Therefore, Claims 1-4, 16, 19, 20, 28, 30, 32-34, and 36 are under consideration. Claim 1 has been amended herein to define the acronym "VLA-1" which was absent from the claim as originally filed. Claim 1 now recites "detecting the presence of Very Late Antigen-1 (VLA-1)." Applicants believe that no new matter was introduced nor new issues raised by these amendments.

Objections to the Specification

The specification is objected to for allegedly not defining the acronym "VLA-1" at its first occurrence on page 1 at line 12. Applicants have amended the specification at page 1, line 12 herein to recite Very Late Antigen-1 (VLA-1). Applicants believe this objection to moot in light of the amendment to the specification and respectfully request its withdrawal.

The specification is objected to because allegedly the word "blood" is misspelled on page 6, line 12. Applicants have amended the specification to correct this error. Applicants believe this objection to moot in light of the amendment to the specification and respectfully request its withdrawal.

Objections to the Claims

Claim 1 is objected to for allegedly failing to define the acronym "VLA-1" in the claim. Applicants have amended Claim 1 to recite "detecting the presence of Very Late Antigen-1 (VLA-1)." Applicants believe this objection to be moot in light of the amendment to Claim 1 and respectfully request its withdrawal.

35 U.S.C 103

Claim 1-4, 16, 19, 20, 28, 30, 32-34, and 36 are rejected under 35 U.S.C. 103 as allegedly being obvious over Braun et al. (2003) *Cytometry Part B (Clinical Cytometry)* 54B: 19-27 in view of Novak et al. (1999) *J. Clinical Investigation* 104: R63-R67. Applicants respectfully traverse the rejection.

In the recent KSR Int'l Co. v Teleflex, Inc. ruling, the Supreme Court has reaffirmed the *Graham* factors for determination of obvious under 35 U.S.C. 103(a). *KSR Int 'l Co. v. Teleflex, Inc. (KSR),* No 04-1350 (U.S. Apr. 30, 2007). The three factual inquiries under *Graham* require examination of: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art. *Graham v. John Deere (Graham),* 383 U.S. 1, 17-18, 149 USPQ 459, 467 (1966). Additionally, the court in Graham noted a fourth consideration for the determination of obviousness would be any objective evidence of secondary considerations such as unexpected results, unmet need in the art, and commercial success.

Furthermore, in order to establish a prima facie case of obviousness, the examiner has the initial burden of supporting the conclusion of non-obviousness. In particular, the Examiner has the initial burden of ascertaining the differences between the claims and the prior art which requires interpreting both the art and the claims as a whole. Put another way, "all words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). Thus, the cited art must still be able to account for all the limitations of the claims otherwise a single reference teaching a single aspect of a claim without further disclosure or knowledge in the art would be able to render a claim obvious and subsequently render all innovation moot. Applicants assert that it is this important consideration that has not been met with respect to the present claims. In fact, no combination of the art cited in the present action can account for all the limitations of claim 1 let alone the additional limitations in the dependent claims.

In particular, Applicants respectfully point out that the cited art alone or in combination fails to teach or suggest that the presence of VLA-1+ antigen specific T cells is indicative of an efficacious immune response. The Examiner asserts that Braun et al. "discloses a method of assessing the activity and analyzing surface receptor expression of CD4+ T cells." Applicants respectfully point out that the Examiner is confusing a subtle yet important distinction between the claims and the prior art. Namely, activation status and efficacy are NOT the same thing. While Braun et al. do analyze CD4 T cells for the presence of various activation markers, at no time is the presence of any one marker investigated or shown to be dispositive of an efficacious immune response.

The Examiner asserts that the CD4+CD103+ cells have elevated levels of VLA-1 in diseased patients relative to normal controls. Unfortunately, Braun et al. never draw this relationship (see page 7, lines 3-5 of the present office action). What Braun et al state in the abstract is that VLA-1 expression is high in CD103+ cells relative to CD103- (negative) cells and on page 19 in the last 4 lines of the left column state that CD4+CD103+ cells are elevated in diseased individuals. Importantly, no showing is ever made of the expression of VLA-1 in normal versus diseased individuals. Because Bruan is silent as to this relationship, no determination can be made as to the relative number or proportions of VLA-1+ cells in normal and diseased individuals. As the Examiner can no doubt appreciate it is entirely possible that the number of CD4+CD103+ cells could increase without there being any change in the number of VLA-1+ cells. Put another way, as the CD4+ cells represents the universe of CD4 cells given a fixed number of cells, the proportion of CD103+ to CD103- cells may change without a similar change in VLA-1. Indeed, as cell surface markers change throughout the activation status of a cell, to say one increases merely because another does is scientific fallacy. For example, although the proportion of CD103+ cells changes, the cells are all still CD4+, CD3+, and CD45RO+ with no apparent change with respect to those markers. .Applicants respectfully point out that this same relationship is also observed in the CD4+CD103-(negative) population. Thus, no particular relationship can be noted by the experiments in Braun with respect to VLA-1.

Furthermore, there is no showing anywhere in Braun to suggest that the VLA-1 positive cells represent a viable pool of immune memory cells. In fact, as Braun et al show that only 40% of the CD103+ cells are also VLA-1 positive (see Table 5), one of skill in the art would have no reasonable expectation that VLA-1 would provide any significant point of distinction much less efficacy. Again, activation status (that is …has antigen been encountered) and efficacy (will the immune response be protective) are not the same thing. VLA-1 is a known activation marker, but its ability to distinguish immune responses that are efficacious from those that are not was not known or otherwise discernable from the teachings in the art. In fact, the authors are quick to point out that they are unclear if the VLA-1 positive cells represent a pro-inflammatory or protective cell population (see page 26, left column, 9 lines form the top). To properly access the prognostic value of a marker, the authors would have had to identify the antigen specific cells (which they did not do), gate their analysis on the antigen specific cells and assess the diference

with and without VLA-1. Braun et al. merely stained with VLA-1 and have no way of knowing if, for example, the VLA-1+CD4+CD103+ cells are also CD28 positive or if the VLA-1-CD4+CD103+ cells represent the CD28+ population. More likely as poor staining technique would attribute for any difference between the CD103+ cells for the remaining markers, it would be impossible to assign any attributable characteristic to VLa-1+ or VLA-1- cells as they appear for all other markers to be the same and no further studies were conducted in Braun to elucidate this difference.

By contrast, Applicants have conducted the necessary experiments to determine the effect of the presence of VLA-1 on a memory T cell population. It is only after reading the present application that one of skill in the art would have in hand the necessary information to see the relationship between VLA-1 and an efficacious immune response. Applicants remind the Examiner of the cautionary warning administered by the Supreme Court against the use of hindsight reasoning. Without the knowledge of the specification, Applicants assert that no reading of Braun will provide all the limitations of the claims much less the appreciation that the presence of VLA-1+ antigen specific T cells is indicative of an efficacious immune response.

Because Braun et al. does not teach or suggest that the presence of VLA-1+ T cells indicates an efficacious immune response, the Examiner must rely on Novak et al. to correct this deficiency. Put another way, the Examiner must rely on Novak et al to rescue the missing limitation so that the cited combination can establish all the limitations in the claims. Applicants respectfully point out that nowhere in Novak et al is VLA-1 discussed as a T cell marker or are VLA-1+ T cells discussed. Accordingly, Novak et al. does not rescue the deficiencies. Because all the limitations in the claims are not disclosed or suggested by either reference alone or in combination, the cited art can not render the present claims obvious. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment authorizing payment in the amount of $555.00 which is the small entity fee under 37 C.F.R. § 1.17(a)(3) for a three (3) month extension of time, and a Request for

a three (3) month Extension of Time are being submitted electronically. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees that may be required or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF EFS-WEB TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted by EFS-WEB on the date indicated below.

/J. Gibson Lanier, Ph.D., 57,519/ — J. Gibson Lanier, Ph.D.

October 8, 2010 — Date